UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/612,852 | 07/10/00 | KRASNYKH V | D6070CIP |

B.C.K

HM12/0919

DR BENJAMIN ADLER
MCGREGOR & ADLER LLP
8011 CANDLE LANE
HOUSTON TX 77071

| EXAMINER | |
|---|---|
| SORBELLO, E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | 3 |

**DATE MAILED:** 09/19/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/612,852 | Applicant(s) KRASNYKH ET AL. | |
|---|---|---|---|
| | Examiner Eleanor Sorbello | Art Unit 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Double Patenting*

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 2, 5, 6, 8, 12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,210,946 (Curiel and Krasnykh). Although the conflicting claims are not

identical, they are not patentably distinct from each other because the claims of the instant application embrace the claimed invention of the Patent No. 6,210,946.

***Claim Rejections - 35 USC § 101***

3. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claim 7 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,210,946. This is a double patenting rejection.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

**The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

6. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adenovirus comprising a fiber replacement protein wherein the protein is T4 bacteriophage fibritin protein which confers a novel tropism and maintains trimerization, does not reasonably provide enablement for an adenovirus comprising any and all fiber replacement proteins that will confer novel tropisms and provide for trimerization. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification teaches the generation of adenoviral vectors comprising a fiber T4 fibritin chimera containing a targeting ligand. The specification provides examples of entry of such adenoviral vectors into 293/6H cells and that 293/6H cells were susceptible to both the adenoviral vectors with the wild type fibers and those adenoviral vectors with a chimeric protein fiber, whereas the progenitor cell line 293 is refractory to Ad5LucFF/6H infection. The specification provides examples wherein the trimerization motif is RGD in the aforementioned vector. The instant specification demonstrates only

one particular replacement protein, the T4 fibritin protein. The specification explains the importance of not interrupting the trimerization of the fiber and retaining proper anchoring (see page 12). It is not clear that replacement of the fiber gene with any gene other than the T4 fibritin gene would allow trimerization and proper association with the penton base protein. However the claims are directed to any chimeric protein that would provide trimerization.

The state of the art with regards the alteration of the natural tropism in order to permit gene transfer to specific cell types is unpredictable due to the inability of the chimeric protein to provide trimerization. Wickham et al. (1997, J. Virol. P. 8221-8229). state that a host cell infection by an Ad involves two of its coat proteins which interact with distinct cellular receptors. Wickham et al. designed several motifs in order to find out the critical factors that determine binding and internalization and found that by using some peptide motifs in this system, they could not isolate viable recombinant vectors. They concluded that the most likely explanation for this was that certain peptide motifs might prevent proper folding of the fiber protein which might be interfering with trimerization. (See page 8221, abstract and col. 1, and page 8228, col. 1).

The claims are however, drawn to any chimeric protein that provides for the trimerization function. In view of the broad claims drawn to any chimeric protein, one of skill in the art will require undue experimentation to make an adenovirus comprising any chimeric protein which will associate with the penton base of the adenovirus and the adenoviral fiber tail and provide for trimerization so that attachment and internalization into a cell of interest will take place.

Because the prior art does not support the use of any chimeric protein that would provide for trimerization, the burden is on the applicant to provide guidance in the specification to support that which is claimed. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

Therefore in view of the state of the art, the breadth of the claims, guidance in the specification and unpredictability in the art, one of skill in the art will require undue experimentation to make and use the invention as claimed with respect to the scope of the chimeric protein that provides trimerization.

Claims 13-15 are directed to the above discussed adenoviruses comprising a therapeutic gene. The instant specification implies no reason to use such a virus except to provide therapy. Claim 15 is directed to a method of using the virus of claim 13 to kill tumor cells in an individual.

Thus, in addition to the above discussion, on the construction of the adenovirus comprising any chimeric protein that provides trimerization these claims are not enabled for the following reasons:

The nature of the invention being gene therapy, the state of the prior art is not well developed and is highly unpredictable. Verma et al. states that out of the more than 200 clinical trials currently underway, very few successes have resulted. (see Verma et al., page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation.

Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al., ¶ bridging pages 81-82.] Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). The instant specification does not provide any *in vivo* working examples.

The specification teaches generically how to construct a therapeutic adenoviral vector comprising a chimeric fiber protein, that has its natural tropism ablated and a novel tropism conferred on it as a result of the targeting ligand, not natural to the adenovirus. However, the specification does not teach targeting ligands specific for cancer cells or ligands that would allow infection of tumor cells. Neither does the specification teach how to deliver the modified adenovirus such that it reaches targeted cells, or that any therapeutic level of expression could be achieved to effect a therapeutic response to any particular disease, specifically cancer.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working

examples provided, and the breadth of the claims that it would require undue experimentation to practice the invention.

***Conclusion***

7. Claims 1-15 are rejected.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eleanor Sorbello whose telephone number is 703-308-6043. The examiner can normally be reached on M-F: 6.30AM-3.00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3230 for regular communications and 703-305-3230 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

September 14, 2001